REMARKS

Status of the Claims

Claims 1-4, 10-22, and 23-25 were pending. Claims 10-18 and 24 are withdrawn from consideration as being drawn to non-elected inventions and claims 1-4, 19-23, and 25 are under active consideration.

Applicants reiterate their request for rejoinder of withdrawn method claims containing all the limitations of the examined composition claims.

Rejections Withdrawn

Applicants note that the rejection under 35 U.S.C. § 112, second paragraph, was not reiterated and is therefore considered withdrawn.

35 U.S.C. § 102

Claims 1-4, 19-21, 23, and 25 were again rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by the reference of Domenighini et al. (International Patent Application WO 93/13202; hereinafter "Domenighini") in view of evidence provided by Pizza et al. (Mol. Microbiol. (1994) 14:51-60). In particular, the Office Action alleges that Domenighini discloses an immunogenic detoxified protein comprising the amino acid sequence of subunit A of an *Escherichia coli* heat labile toxin (LT-A) having the mutations Ser63Lys and Arg192Asn and a vaccine composition comprising this protein (Final Office Action, pages 2-3). The Office Action further alleges that Domenighini inherently anticipates the instantly claimed invention in light of evidence provided by Pizza (1994) showing that Lys63 causes loss of toxicity (see Table 1 and 2) and the Arg192Asn substitution decreases the rate of proteolysis and activation *in vivo* (Office Action, page 7). Applicants respectfully traverse the rejection.

Anticipation is a rigorous standard -- the cited reference must teach every aspect of the claimed invention either explicitly or implicitly. See, e.g., M.P.E.P. § 706.02. Applicants respectfully submit that Domenighini (as evidenced by Pizza) does not teach all aspects of the Applicants invention, either explicitly or implicitly.

Claim 1 (from which all other claims directly or ultimately depend) is drawn to a non-toxic, immunogenic mutant form of a CT or LT protein in which both the amino acids at the position corresponding to Ser-63 of SEQ ID NO:7 and Arg-192 are replaced with another amino acid. It does not relate to toxins with only one of these mutations – both must be present.

Domenighini does not teach that both Ser-63 and Arg-192 should be mutated in the same protein. Indeed, Domenighini directs the skilled artisan to make mutations in Val-53, Ser-63, Val-97, Tyr-104 or Pro-106. See, claim 1. Dependent claim 2 indicates an additional 14 amino acid residues that can be subject to mutation. However, none of the above mutations or combination of mutations is indicated as being preferred over the others. The combination of claim 1 (5 mutations) and claim 2 (14 mutations) is therefore, at best, a notional generic disclosure of 70 different double mutations (5x14=70). None of the 70 is indicated as being preferred over another in any way.

In order to show that Domenighini anticipates the pending claims, the burden is on the Office to show that the claimed compositions can be immediately envisaged by the skilled artisan from Domenighini. A reference embracing a large number of species cannot be said to necessarily anticipate a particular species. See, *In re Meyer*, 599 F.2d 1026, 202 USPQ 175 (CCPA 1979); *Akzo N.V. v. International Trade Comm'n*, 808 F.2d 1471, 1 USPQ2d 1241 (Fed. Cir. 1986). In the instant case, the particularly claimed species recited in the claims is not only a double Ser-63/Arg192 mutant, the protein must also be immunogenic and detoxified. Domenighini does not describe toxicity of this double mutant. Moreover, Domenighini teaches that the Arg-192-Asn mutant retains wild-type toxicity. See, page 46, Table I, row O of Domenighini.

Still further evidence that the skilled artisan would not immediately envisage the specifically claimed detoxified double mutant from the 70 possibilities allegedly disclosed is found in Magagnoli et al. (Ref. C25 of IDS submitted March 16, 2004). In particular, Magagnoli et al. teaches that another double mutant (Val97-Lys and Arg7-K) "suggested" in claims 1 and 2 of Domenighini is more toxic than "detoxified" single mutant (Val97). Specifically, Magagnoli shows that the Val97-Lys single mutant becomes toxic at 38.8 ug/ml while the Arg7-K single mutant is toxic at 1.9 ug/ml. When

the two mutants are combined in a single protein, the mutant protein is toxic at 7.9 ug/ml. Thus, Magagnoli evidences that a double mutant containing one detoxifying mutation and one toxic mutation is not necessarily detoxified.

In light of the state of the art teaching that double mutants are toxic even when they include a single mutation that, by itself, renders the protein detoxified (*e.g.*, Magagnoli), the skilled artisan would not "immediately envisage" that a double mutant as claimed would necessarily be detoxified. Accordingly, Domenighini does not anticipate the pending claims.

Furthermore, the allegation that Pizza et al. discloses that Arg-192Asn mutation "decreases the rate of proteolysis and activation *in vivo*" does not in any way disclose the claimed double mutants or indicate their toxicity. Rather, Pizza states that the Arg-192Asn mutant was fully toxic (see, Pizza, page 57, 1st paragraph):

> ...this mutant was found fully toxic, suggesting either the substitution did not affect proteolysis at all, or that the rate of proteolysis was only decreased to a level that did not affect toxicity *in vivo*.

Therefore, claim 1 and all claims dependent therefrom are not anticipated by Domenighini, and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

35 U.S.C. § 103

Claim 22 was again rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Domenighini et al. (*supra*) in view of the reference of Clements et al. (U.S. Patent No. 6,019,982; hereinafter "Clements"). Domenighini is cited for teaching DNA molecules that encode mutant detoxified heat labile toxin of *E. coli* and mutant detoxified cholera toxin having mutations in the A subunit at positions 63 and 192. It was acknowledged that Domenighini fails to disclose an Arg192Gly mutation. Clements is cited for teaching the Arg192Gly mutation. The Office Action alleges:

> It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to modify the mutation of Domenighini at position 192 from Asn to Gly as taught by Clements, because Clements and Domenighini et al. are both directed to the site directed mutagenesis of heat labile toxin of E. coli at position 192, and Clements et al. teach the advantage of substituting Gly at position 192 as yielding a stable, detoxified mutant that is devoid of ADP-ribosyl transferase activity, but retains its activity as an immunological adjuvant (see Clements, col. 8, lines 24-27 and 28-50). (Final Office Action, page 5)

Applicants respectfully traverse the rejection under 35 U.S.C. § 103 and the Office Action remarks and purported facts underlying the rejection on the following grounds.

As noted previously, the Office has failed to provide evidence that the claimed invention is a "predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. ___, 127 S. Ct. 1727 (2007). In addition, Applicants note that secondary considerations such as unexpected results must be considered in determining obviousness. See, also, Patent Office "Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Fed. Reg. Vol. 72, No. 195, October 10, 2007"):

> Objective evidence relevant to the issue of obviousness must be evaluated by Office personnel. Such evidence, sometimes referred to as "secondary considerations," may include evidence of commercial success, long-felt but unsolved need, failure of others, and unexpected results. For at least these reasons, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

In the instant case, the cited art fails to provide evidence that a double mutant as claimed would not only retain immunogenicity, but also be detoxified and more resistant to trypsin proteolysis than wild type CT-A or LT-A. Moreover, the evidence of record establishes that it was unexpected that a double mutant as claimed would exhibit reduced toxicity in light of the fact that one of the mutations resulted in a toxic protein.

The primary reference of Domenighini fails to disclose all of the elements of the pending claims, namely an immunogenic detoxified LT-A protein having amino acid substitutions at both Ser-63 and Arg-192. As noted above, the art (*e.g.*, Magagnoli) teaches that a double mutant is not necessarily detoxified when it includes a mutation that is, by itself, toxic. Thus, it is entirely surprising and unexpected that combining a single detoxified mutant (K63) and non-detoxified single mutant (G192) in the same protein results in double mutant with reduced toxicity as compared to the single detoxified mutant and which is more resistant to proteolysis than the K63 mutant.

In view of the perceived toxicity of the Arg192Asn mutant and double mutants containing toxic single mutants, Domenighini would have motivated the skilled artisan to combine the Ser63Lys mutation with substitutions at position 192, as claimed. Therefore, Domenighini fails to provide any reasonable expectation of success that the combination of the two substitutions at Ser-63 and Arg-192 would produce a more stable, detoxified immunogenic LT-A protein.

Furthermore, Clements fails to teach or suggest that mutations should be made to more than one residue of LT-A. Clements fails to make mutations in other positions or suggest that multiple mutations would be desirable.

In view of the clear teaching away by Domenighini and failure of Clements to teach multiple mutations, one of skill in the art would have had no reason to combine Clements and Domenighini to arrive at the claimed invention and a *prima facie* case of obviousness has not been and cannot be established.

35 U.S.C. § 112, first paragraph, enablement

Claims 1, 3, 4, 19, 23, and 25 were again rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not provide an enabling disclosure commensurate in scope with the claims. (Final Office Action, pages 8-10). In particular, the Office Action alleges "the specification, while being enabling for immunogenic, detoxified proteins comprising the amino acid of subunit A of an *E. coli* heat labile toxin (LT-A) wherein the amino acids at positions Ser-63 and Arg-92 of SEQ ID NO:7 are replaced with another amino acid, and further wherein the amino acid at position Ser-63

is replaced with Lys-63 and the amino acid at position Arg-192 is replaced with Asn-192 or Gly-192, does not reasonably provide enablement for immunogenic, detoxified proteins comprising **any** amino acid replacement at Arg-192 as instantly claimed." (Final Office Action, pages 9-10). The Office Action cites Rudinger et al. (1976) in support of the position that "even a single amino acid difference may account for markedly different biological activities" (Final Office Action, page 9).

Applicants respectfully traverse the rejection.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Applicants respectfully submit that the current claims indeed comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. The as-filed specification clearly teaches the claimed double mutants in which any amino acid residue is substituted for the specified Ser63 and Arg192.

In this regard, the Examiner has indicated that Park et al. (1999) Exp. & Mol. Medicine 31(2):101-107), submitted in an IDS with the previous response does not show that the properties of mutations to Ser63 other than those exemplified can be extrapolated to a certain degree. In fact, Park's post-filing date article showing that substituting Tyr for Ser resulted in a detoxified LT mutant clearly demonstrates that the as-filed specification is enabling for any substitution at the indicated positions.

Thus, contrary to the Examiner's assertion, Park clearly establishes that the guidance in the specification more than amply enables the skilled artisan to make any substitution at the recited positions and that such substitutions result in the detoxified

proteins. Applicants are not required to exemplify each and every substitution. All that is required is that the specification teaches the skilled artisan how to make and use the claimed proteins.

Furthermore, the trypsin cleavage site of LT was well-known at the time of filing, therefore, it is reasonable to expect that the properties of the exemplified Arg192 mutants are shared by other mutants which remove the trypsin recognition sequence. The present disclosure lies in recognizing that mutations at these two positions give rise to a more stable and more immunogenic protein, not in the specific mutations at these positions.

Clearly, given the guidance in the as-filed specification and state of the art regarding how to make amino acid substitutions at the 2 indicated residues and how to test the resulting proteins for toxicity, the skilled artisan could readily make and use the claimed proteins without undue experimentation. Contrary to the Examiner's statement, "expensive and time consuming" experimentation is not necessarily undue. See, M.P.E.P. § 2164.06 stresses that time or expense do not establish that experimentation is "undue" even when the specification exemplifies only one embodiment, but sets forth detailed methods of finding alternative embodiments (see, MPEP § 2164.06):

> In *United States v. Telectronics*, Inc., 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989), the court reversed the findings of the district court for lack of clear and convincing proof that undue experimentation was needed. The court ruled that since one embodiment (stainless steel electrodes) and the method to determine dose/response was set forth in the specification, the specification was enabling. The question of time and expense of such studies, approximately $50,000 and 6-12 months standing alone, failed to show undue experimentation.

Thus, following the guidance set forth in detail in the specification regarding amino acid substitutions and assaying for toxicity, the skilled artisan could readily design, produce and test any detoxified, immunogenic Ser63/Arg92 double mutant. Accordingly, because the experimentation required to make and use double mutants as claimed is not undue, withdrawal of the rejection is respectfully requested.

For all the foregoing reasons and the reasons of record, withdrawal of the enablement rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

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Respectfully submitted,

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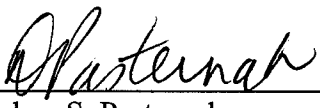
By: 

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